

## **AMENDMENTS TO THE SPECIFICATION**

**Please replace the CROSS-REFERENCE TO RELATED APPLICATION section on page one with the following amended CROSS-REFERENCE TO RELATED APPLICATION section.**

This application is a non-provisional application claiming priority to its corresponding provisional application No. 60/412,227 filed Sep. 20, 2002. This application is a continuation-in-part of non-provisional U.S. application ~~interim~~ serial no. 10/662,884, filed ~~Aug 25~~, **Sept 16**, 2003. Both the above-noted provisional and non-provisional applications are incorporated herein by reference in their entirety.

**Please replace the paragraph [457] in Example 1 with the following amended paragraph [457].**

Maintenance (below a desired level – e.g.,  $\leq 6\%$  by weight of total weight) or decrease of aggregate levels of B-2036 PEG was accomplished by using BI (the Bulk Intermediate B-2036) as the starting material prepared as indicated in non-provisional U.S. patent application ~~interim~~ serial no. ~~P-107,891~~ **10/662,884** entitled Method for the Production Of Growth Hormone And Antagonist Thereof Having Lower Levels Of Isoform Impurities Thereof, filed ~~August 25~~ **September 16**, 2003 before the U.S. Patent and Trademark Office. Fermentation (to yield B-2036) in a recombinant *E. coli* expression system was carried out as described by Cunningham et al. in U.S. Patent No. 5,849,535. Purification of B-2036 BI was performed as described by the above-identified non-provisional U.S. patent application no. (~~P-107,891~~) **(10/662,884)**. This material was then processed using the initial pegylation and hydrophobic interaction chromatography steps as noted in flowchart 1 below to produce B-2036 PEG. Following the hydrophobic interaction chromatography (step 2), the B-2036 PEG was UF/DF into pH 7, 25 mM TRIS buffer (instead of pH 4 sodium acetate buffer as in the process of Example 2, step 3, flowchart 2). The retentate was then subjected to Q Sepharose

FF column strong anion exchange chromatography. This step separates differentially PEGylated species into fractions for pooling to achieve the PEGylated species distribution required for API release. This column enriches for the PEG-4, PEG-5 and PEG-6 products of PEGylated BI (B-2036 PEG). The product is eluted with a 20 CV linear gradient from 0-250 mM NaCl in 25 mM Tris, pH 7.0 following equilibration steps and a 2 CV wash with 25 mM Tris, pH 7.0. Analysis of fractions is accomplished using CE instead of SDS-PAGE as noted in Example 2, flowchart 2. See previous discussion regarding same. Pegvisomant (Somavert<sup>®</sup>; Pharmacia) is collected from the chromatography profile as a pool from fractions analyzed by CE with a pooling criteria of  $\geq 75\%$  PEG4+5+6 (first fraction) and  $\geq 94\%$  PEG4+5+6 (last fraction) and  $\geq 0.5$  mg/mL. The resulting product was then carried through the remainder of the B-2036 PEG purification process as described in flowchart 1. After selection and pooling of the fractions, the analysis of the pooled material and final API by SEHPLC showed no detectable aggregate. See Table 1 indicating the same below.